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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,137	03/11/2002	Kelvin Stott	P67518USO	8173

136 7590 12/28/2004

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

JACOBSON HOLMAN PLLC
Response Due On Or Before
3 / 28 / 05
Month Day Year

EXAMINER	
LIU, SAMUEL W	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Attn: Examiner Weber
(571) 273-0925

Office Action Summary	Application No.	Applicant(s)
	10/030,137	STOTT, KELVIN
	Examiner	Art Unit
	Samuel W Liu	1653

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-18-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-28 and 43 are pending.

Applicants' amendment filed 18 October 2004, which cancels claims 29-42 and 44-45, and amends claims 1-28 has been entered. Also, applicants' request for extension of time of one month (filed 18 October 2004) has been entered.

Please note that the objection(s) and/or rejection(s) not explicitly stated and/or restated below are withdrawn.

IDS

The references of IDS filed 18 December 2004 have been considered by Examiner.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-28 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 as amended does not make it clear as to whether or not the characteristics of said four consecutive α-L-amino acid residues set forth in item c refer to the first edge only, or the second edge, or both of the first and the second edges. The dependent claims are also rejected.

In claim 18, the recitation "a mimic thereof" is indefinite because it is not clear regarding whether or not the "mimic" refers to the mimic of the claimed compound or the mimic of the peptide set forth in the claim.

Claim 28 is indefinite in "N- or C-substituted form" because it is not apparent as to whether or not it refers to a substituted form at Nα (backbone nitrogen) or backbone carboxyl moiety, or, refers to N-terminal or C-terminal substituted form.

The applicant's response to the rejection under 35 USC 112, second paragraph

~~The response filed 18 October 2004 argues that~~

On page 35, the response discusses that claim 12 recitation "extends beyond" has been defined in the specification on page 29, lines 20-30. The applicants' argument is found to be not persuasive because the specification provides insufficient definition for the phrase "extends beyond". The phrase can be regarded as an action via a *covalent* or *non-covalent* chemical bonding. Note that the specification only describes "extended side chain" but not "extends beyond" *per se* in said page.

On page 36, the response argues that claim 28 recitation is clear as the specification defines the alternative peptide backbone substitution (page 9, line 21 to page 10, line 5). The applicants' argument is found to be unpersuasive because pages 9-10 of the specification do not provide sufficient definition for "N- or C-substituted groups" per se. Thus, the claim should make it clear that the group set forth in item *b* of claim 28 refers to (i) amino terminal N-, or/and a backbone N-substituent, or, (ii) carboxyl terminal C- or/and a backbone carboxyl C-substituent.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 4-13, 15-18 and 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Quibell M. et al. (*J. Chem. Soc. Perkin. Trans* (1995) 1, 2019-2024) as is evidenced by the known facts (i)"KLVFF" is a consensus sequence contributed to β-strand interaction taught by Tjernberg, L. O. et al. (*J. Biol. Chem.* (1997) 272, 12601-12605, from IDS filed 18 October 2004); and (ii) proteolysis-resistance is an *inherent property* of the Nα-substituted polypeptide) disclosed in the reference by Miller S. M. et al. (*Drug Dev. Res.* (1995) 35, 20-32).

Quibell et al. teach a peptide compound comprising (*i*) a peptide portion (residues 16-33) that is capable of forming β-structure on its *N-terminal* region (*equivalent to the first edge of the instant application*) wherein "KLVFF" (residues 16-20, depicted in the polypeptide sequence on

page 2020) is a β-strand forming core sequence, and, wherein Phenylalanine residue (F) 20 is Nα-substituted with N-(2-hydroxy-4-methoxybenzyl), *i.e.*, Hmb), and (*ii*) a peptide portion (residues 34-42) located at the C-terminal section of the polypeptide (*equivalent to the second edge of the instant application*) wherein residues 34-36 and 39-42 participate in β-strand interaction as depicted in Figure 1 (*see especially "cross "X" symbol which indicates intermolecular β-strand interaction*). The above mentioned the Quibell's polypeptide has the following characteristics: (1) comprises at least four consecutive α-L-amino acid residues (e.g., "KLVFF" motif) which are able to form non-covalent interaction with neighboring side chains of the target β-strand (e.g., other amyloid β-strand molecule) as is evidenced by Tjernberg et al. reference; and, (2) within said motif there is at least one residue is Nα-substituted (i.e., Phe20). Note that the β-amyloid polypeptides are of prone of forming interchain β-strand interaction, and the "KLVFF" motif resides in said β-amyloid. There therefore exists interaction between the target β-strand and the β-strand forming section of the peptide (see "*... substantial improvement in the quality of the β-amyloid(1-43) crude product*" on page 2020, the left column, the 2nd paragraph of the Quibell' reference). Thus, the above Quibell's teachings anticipate the instant claims 1 and 15.

The Quibell's peptide compound is made for preventing hydrogen boding between β-structures of individual polypeptides (i.e., interchain interaction) thereby inhibiting intermolecular aggregation of the said polypeptides (see page 2019). The Hmb-modification of the β-amyloid peptide (consisting of 34 residues) promotes formation a β-strand and hinds the β-

amyloid aggregation (see the above statement). The above Quibell's teachings anticipate the instant claims 4 and 7.

Since the current application is directed to composition, and since proteolysis-resistance is an *inherent property* of the claimed composition as is evidenced by Miller et al. reference, the above Quibell's teachings are applied to the instant claim 5.

Since claim 6 recites the limitation that the Nα-substituted group is "a group that is connected to the Nα atom by a CH_2 (methylene) group", and since the Quibell's peptide compound contains CH_2– group in N-(2-hydroxy-4-methoxybenzyl) wherein said CH_2– group is linked to Nα atom of peptide backbone (see structure depicted on page 2019), the above Quibell's teachings anticipate the instant claim 6.

In the above mentioned "KLVFF" motif, residues Leu, Val, and Phe have β-sheet formation propensity > 1.00, which anticipates the instant claim 8.

Quibell et al. teach that the β-forming peptide comprising the "KLVFF" motif has amino acid side chains that promote β-structure formation, e.g., 3-methylvaleric group (Leu), isovaleric group (Val), methyl group (Ala) and 3-methylvaleric group (Ile); these groups have hydrophobic characters and high propensity of forming β-structure. The Quibell's teaching anticipates the instant claims 9-10.

Quibell et al. teach that the β-strand forming peptide contains glycine residues (see page 2020 and Figure 1) which hinder the β-strand stacking because glycine has no said chain, which anticipates the instant claim 11.

Figure 1 (*a*) shows a neighboring side chain interaction in secondary structure of the β-forming polypeptide , which anticipates the instant claim 12.

In "*Results and Discussion*" section, Quibell et al. teach the β-forming peptide comprising Hmb-substituents is detected and analyzed by HPLC-assisted electrospray mass spectrometry (see page 2020, the left column), wherein the Hma group gives rise to a characteristic peak in the mass spectrometric profile (see Figure 2). Thus, the Quibell's teaching anticipates the instant claim 13.

Quibell et al. teach that the Nα-substituted (Hmb-modified) polypeptide inhibits aggregation of β-amyloid (i.e., Alzheimer's Aβ peptide); the Quibell's polypeptide comprises "KLVFFAE" (see peptide structure in page 2020). Because the inhibition requires the polypeptide direct interaction with target β-strand (i.e., the Aβ peptide), the Quibell's teaching anticipates the instant claims 16-17.

Because the subsequence "KLVFFAE" (residues 16-22) of the Quibell's polypeptide meets all the limitations set forth in claim 18, the Quibell's teachings anticipate the instant claim 18.

The N-terminus of the Quibell's peptide is unmodified, i.e., comprises free N- and C-termini, which anticipates the instant claim 22.

In Figure 1 (*a*), the Quibell's ypeptide is attached to a resin, which anticipates the instant claims 23-24 (note that claim 24 sets forth the limitation that the functional component is a resin).

Quibell et al. teach that the above said polypeptide attached to the resin through C-terminus of the polypeptide, which anticipates the instant claim 25.

Also, Quibell et al. teach that the Hmb-substituted polypeptide inhibits (i.e., interacts with) β-amyloid which comprises "KLVFF" sequence, which anticipates the instant claim 26.

Further, Quibell et al. teach that adjacent to the "KLVFF" motif, Gly 25 is Hmb-substituted (see page 2020 peptide structure), because the Hmb-substituted glycine mimic phenylalanine (F), the Quibell's teaching meets the limitation set forth in the instant claim 27.

Since the above mentioned Gly 25 Hmb-substituent has similar stereochemistry of said chain of phenylalanine and allows for a β-strand interaction, the above Quibell' teaching anticipates the instant claim 28.

The applicant's response to the rejection under 35 USC 102

The response filed 18 October 2004 discusses the first edge and the second edge of the claimed composition (pages 37-39) and infers that N-terminal region and C-terminal region is not said edges. The applicants' argument is not persuasive because the instant disclosure does not specify the edges, and because the Quibell's polypeptide structure indicated above meets the limitation, i.e., "a first edge and a second edge, corresponding to opposite sides of said peptide backbone" set forth in item *a* of claim 1.

In pages 39-42, the response discusses the issue regarding comparison of function/activity (e.g., inhibition of aggregation) of the Quibell's polypeptide compound with the instant compound, and discusses involvement of Gly 37 residue in β-structure (β-turn) formation, and infers that Quibell et al. do not disclose the chemical compound comprising a peptide that comprises a β-strand-forming section which has the two edges, one of which associates with a target β-strand, and one of which comprises at least four α-L-amino acids wherein at least one of said amino acids is Nα-substituted set forth in the claims (see page 42, the second paragraph). The Applicants' argument is found to be unpersuasive because (i) the

Quibell's polypeptide meets all the limitations set forth in claim 1 and the rejected claims which depends form claim 1 (see the above statement in the rejection section); (ii) N- and C-terminal regions the Quibell's polypeptide meet the limitation "the two edges" wherein "KLVFF" motif (resides in N-terminal region) of the Quibell's polypeptide comprises one Nα-substitution (i.e., Hmb-Phe 20); thus, Quibell et al. teach all structural features (limitations) set forth in the instant claims; and (iii) in the Quibell reference, Gly 37-Hmb substitution acts on improving solubility of the Quibell's polypeptides by reducing interchain interactions occurring between β-hairpin structures in which Gly 37; this thus would assist the subsequence comprising "KLVFF" motif in view of interaction with a target β-strand(s).

Please note that the current invention is directed to a composition comprising the polypeptide, and that structural feature thereof is *inherent* property of the polypeptide; the Quibell' polypeptide which contains the said motif comprising the Nα-substituent (Hmb) has ability of forming β-strand or/and participating in β-strand interaction as set forth in the claims of the current application. Also, it is of note that products of identical chemical composition cannot have mutually exclusive properties (e.g., herein, forming β-strand or/and participating in β-strand interaction). A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

The following is a new ground of rejection

Claims 1, 4-10, 13-18, 22-28 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Kelly, J. W. (US Pat. No. 6034211) as is evidenced by the known fact that proteolysis-resistance is an *inherent property* of the Nα-substituted polypeptide) disclosed in the reference by Miller S. M. et al. (*Drug Dev. Res.* (1995) 35, 20-32, provided by the IDS filed 18 October 2004).

In the patent claim 1, Kelly teaches a chemical compound, i.e., a β-sheet peptidomimetic comprising (i) the first peptide (*recognition strand*) of 3 to 21 amino acid residues which further comprises a recognition sequence that interacts with a target protein which self assembles (e.g., β-amyloid protein (see column 11, lines 37-43, and column 12), and (ii) a second peptide (*blocking strand*) of 3 to 21 amino acid residues which further comprises Nα-substituted residues, e.g., N-methylated residue. The kelly's compound has the structural characteristics of the composition of the instant claim 1, i.e., (1) the first peptide is able to associate with a target β-strand; (2) the first and the second peptides are β-forming sequences (see Scheme II depicted on columns 13-24) and N-methylated (see column 13, lines 18-20); (3) the said β-forming sequence comprises a subsequence wherein at least one in every 8 residues is N-methylated (see column 14, lines 1-3), and wherein the said residues are α-L-amino acids; and (4) the Kelly's patent is directed to an inhibitor of β-strand aggregation (see column 14, lines 25-40) which inhibits amyloid protein assembly (see column 23, lines 43-57). The Kelly's patent therefor anticipates the instant claim 1.

Please note that the above said the first and the second peptides are corresponding to the first edge and the second edge of the peptide of the instant application, respectively; and that

That, in item *c* of claim 1, the recitation "at least one of which is substituted with an Nα-substituent" excludes the limitation set forth in item *d* of the claim which requires more two successive Nα-substituents thereof. Thus, the Kelly's patent is an anticipatory art over the current invention.

The Kelly's compound depicted in the Scheme II (columns 13-24) shows the said Nα-substituents allow β-strand formation, which anticipates the instant claims 4 and 7.

Since the current application is directed composition, and since proteolysis-resistance is an *inherent property* of the said composition (i.e., compound comprising Nα-substituted polypeptide) as is evidenced by Miller et al. reference, the above Quibell et al. teachings are applied to the instant claim 5.

In the Kelly's compound, N-methylation is conjugation of a methyl group to Nα, which anticipates the instant claim 6.

The β-forming strand of the blocking strand of the Kelly's compound comprises valine, leucine and isoleucine (see the patent claim 1, item c), all of which have β-sheet formation propensity > 1.00, which anticipates the instant claim 8.

Kelly et al. teach that the first and the second peptide strands comprise β-strand forming sections which participate in non-covalent interaction, e.g., hydrophobic interaction (see column 11, the 4th paragraph), which anticipates the instant claims 9-10.

In column 25, lines 31-37, Kelly et al. teach a radiolabled compound in order to allow the compound to be detectable, which anticipates the instant claim 13-14.

In the patent claim 1, Kelly et al. teach that the amino acid residues in the β-strand forming section are valine, leucine and isoleucine, which anticipates the instant claim 15.

Kelly et al. teach that the recognition strand of said compound interacts with a recognition sequence (i.e., target molecule): KLVFF (SEQ ID NO:19) from β-amyloid, which anticipates the instant claims 16 and 26.

Since the target molecule (β-stand) is component of Alzheimer's β-amyloid (see column 23, the left column, the last paragraph), which anticipates the instant claim 17.

Since the β-stand forming peptides of the Kelly's compound comprises 4 amino acid residues KIFY (Lys-Ile-Phe-Tyr, see SEQ ID NO:13, columns 13-14), which anticipates the instant claim 18.

The Kelly's β-structures depicted in Scheme II (columns 17-18) shows the structures have a free N-terminus and an amidated C-terminus, which anticipates the instant claim 22.

Tin the kelly's compound, the β-strand(s) is linked to a functional group, diarylheterocycle (see the patent claim 1 and Scheme II), which anticipates the instant claim 23.

Kelly et al. teach that the compound (a β-turn mimic) promotes interstrand interaction between the compound and target sequence (recognition sequence) in a highly favorable conformation for binding to the said target protein (see column 10, lines 1-17), which anticipates the instant claim 24.

In the Scheme II (columns 15-18), Kelly et al. shows that linkage of the β-strand forming section of the compound to said functional group through an amide bond, which anticipates the instant claim 25.

Kelley et al. teach a modified component, i.e., ornithine (Orn) in the β-strand forming portion of the Kelly's compound (see Table 1), which anticipates the instant claim 27.

Also, Kelley et al. teach a pharmaceutical composition comprising the (patent) claimed compound (see column 24, the 2nd paragraph), which anticipates the instant claim 28.

The provisional rejection under 35 U.S.C. 101, Double Patenting, is withdrawn because the 1003138 application is directed to α-D-amino acids rather thanα-L-amino acids.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.

Art Unit 1653, Examiner

December 21, 2004

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/160,352	05/30/2002	Cristina Alonso-Alija	Le A 35 361	1397

7590 10/01/2003

Jeffrey M. Greenman
Vice President, Patents and Licensing
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKETED
RESPONSE DATE 1/1/2004
ACTION REQUIRED Respond to O.A.
PERIOD Extendible 2/1/2004
3/1/2004 & 4/1/2004

Office Action Summary	Application No. 10/160,352	Applicant(s) ALONSO-ALIJA ET AL.	
	Examiner Sudhaker B. Patel, D.Sc.Tech.	Art Unit 1624	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' communication paper # 6 dated 5/30/02 is acknowledged.

Applicants have cancelled claims 6, 8, amended claims 1-5,7,9,10. The3refore the claims in this application are the claims 1-5,7,9,10.

After further review and consideration, this application is found not ready for allowance at this stage for the reasons stated bellow.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 10/7/02 and also on 10/21/02 as paper # 4 and 5 are being considered by the examiner. Signed copies of PTO Form 1449 are enclosed with this communication for applicants' record.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims1-5, 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

4. Claim 1 recites: " A compounds of Formula (I) and its salts, hydrates and/or solvates". It is not very clear as to what applicants want to claim exactly. A compound and its salts make it a mixture. Correction to:" A compound or its salts" is required.

5. Claim 1 recites: " A compounds of Formula (I) and its salts, hydrates and/or solvates". The term and/or is not acceptable. Correction to "or" is required.

6. Claim 1 recites R1 component as:" C6-C10 aryl optionally substituted" and also " 3-10 membered carbocyclyl, which is optionally substituted". It is not very clear as to which aryl or carbocycliyl ring and how many substituents onto each ring.

7. Claim 4 recites:" Preparation of a compound of claim 1 by reaction of compound (IV) with a dehydrating agent". It is not exactly clear as to what applicants want to present with. Dehydrating agent will remove a molecule of H2O. In the instant compound (IV) to be converted into a compound of claim 1, the side chain—C (H)(alkyl)-NH-CO-R2 will only form an enolic form "-C (H)(alkyl)-N=C (OH)-R2, and this has to react further to get attached to N of the triazin-one core, and the N has no extra H".

8. Claims 9, 10 recite:" and/or". This is not acceptable. Ex parte Anderegg, 51 USPQ 66.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9,10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating asthma, does not reasonably provide enablement for preventing inflammatory processes and/or immune diseases. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

11. Enablement for the scope of "inflammatory diseases" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

12. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together,

typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

13. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulites is inflammation of the tissues around eye, and Orbital cellulites is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

14. Specification of page 14 recites varios diseases. These include, immune diseases, inflammation of gastro-interstinal tract, bone resorption disease, Crohn's disease, type I diabetes mellitus, psoriasis, atopic dermatisis, vernal conjunctivitis, arterial restenosis, sepsis, shock, allograft rejection, malaria, AIDs, prevention of tumor growth and tissue invasion, depression, memory impairment, and diseases yet to be discovered.

15. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

16. ***Following references are cited to show the state of art:***

Mechanism of diseases formed by inflammation:

Granata et al (PubMed Abstract 12876405, also cited as Int. Arch. Allergy Immunolo. 131/3,153-63(2003)) state that: " Therefore, sPLA (2) s **may** have an important role in inflammatory allergic reactions by activating multiple mechanisms within inflammatory and immune cells, leading to production of eicosanoids, cytokines and chemokines".

Status of current clinical trials:

Scott et al (PubMed Abstract 12783578, also cited as Expert Opin Ther.Targets, 7/3,427-40(2003)) state that:" However, progress in our understanding of the functional role of the ten secreted enzymes..phospholipid(PL) metabolism and in eicosanoid-mediated disorders, together with their emerging activity-independent and receptor-mediated functions, **is likely** to cause significant impact on current and future drug development efforts".

State of affairs with Reference compound Cilomilast's clinical trials:

Giembycz MA.(PubMed Abstract 11772257, also cited as Expert Opin Investig. Drugs, 10/7,1361-79 (2001)) states that:" The compound displays a promising clinical profile in the treatment of inflammatory airway... COPD and results of further Phase III trials are awaited with interest".

BAY 19-8004/PDE4 inhibitors for the treatment of COPD:

Sturton et al(PubMed Abstract 12010850, also cited as Chest. 121/5, 192S-196S(2002)) state that:" BAY 19-8004 which is a novel compound for treating COPD, awaits further long term clinical trials".

PDE4 and its role in inflammatory processes:

Jacob C. et al(PubMed Abstract 12185965, also cited as Therapie, 57/2,163-8,(2002)) state that:" PDE4 inhibitors have been demonstrated to be very potent in the treatment of chronic inflammatory diseases like asthma or chronic obstructive pulmonary disease(COPD) but their therapeutic window is yet to be improved".

Discussion about non-steroidal anti-inflammatory agents:

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications(Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of the causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

17. Specification on pages 16-19 recites various tests and assay method for inhibition activity of PDE4. Results recited in lines 21-22 of page 17 state that:" The preparation examples had IC50 values within the range of 0.1 nM - 10000 nM.

These results will only serve for the preliminary screening of many compounds, and not for treating or preventing the diseases as claimed herein.

18. The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical

arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to inflammation.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to control or prevent disorders related to inflammation

19. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

Allowable Subject Matter

20. Claims1-5,7 related to compounds, composition and a method of making Formula (I) would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and others, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

21. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art of record reference Hartley et al(U.S.P. 4278673)) teaches imidazo-1,2,4-triazin-4(H)-one which possess spasmolytic and cAMP phosdiesterase inhibitory activity. The ref.' 673 differs from the instant compounds by having 7-position of imidazo-1,2,4-triazine-4-one core substituted by R4 = methyl, propyl or isobutyl or cycloalkyl group, and not specifically similar to instant R2 which is 4-tertrt-butyl-

cyclohexyl-1-yl-.. The ref. '673 does not indicate or suggest to arrive at the instant compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm.' Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at 703 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

SP/-
September 30, 2003

DEEPAK R/O
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/160,352	Applicant(s)/Patent Under Reexamination ALONSO-ALIJA ET AL.	
	Examiner Sudhaker B. Patel, D.Sc.Tech.	Art Unit 1624	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4276873	07-1981	Hartely et al	424/249
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Granata et al,PubMed Abstract 12878405, also cited as Int. Arch. Allergy. Immunol., 131/3,153-63(2003).
	V	Scott et al, PubMed Abstract 12783578, also cited as Expert Opin. Ther. Targets, 7/3,427-40(2003).
	W	Giembycz MA., PubMed Abstract 11772257, also cited as Expert Opin. Investig. Drugs,10/7,1361-79(2001).
	X	Strurton et al, PubMed Abstract 12010850, also cited as Chest, 121/5,192S-196S(2002).

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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FOREIGN PATENT DOCUMENTS

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	S					
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	V	
	W	
	X	

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